PATENT CLAIMS

1. A modified molecule having the biological activity of staphylococcal enterotoxin B (SEB) and being substantially non-immunogenic or less immunogenic than any non-modified molecule having the same biological activity in an individual when used *in vivo*, wherein (i) the said loss of immunogenicity is achieved by removing one or more T-cell epitopes derived from the originally non-modified molecule and said T-cell epitopes are MHC class II ligands or peptide sequences which show the ability to stimulate or bind T-cells via presentation on class II,
(ii) said modified molecule, when tested as a whole protein in a biological human T-cell proliferation assay, exhibits a stimulation index (SI) smaller than the parental non-modified molecule and smaller than 2.0, and
(iii) said T-cell epitopes to be removed are located on one or more strings termed R1 to R3 of contiguous residues of the originally non-modified SEB molecule, the strings are selected from:

R1: KFTGLMENMKVLYDDNHVSAI;

R2: QFLYFDLIYSIKDTKLGNYDNVRV;

R3: NKDLADKYKDKYVDVFGANYYYQCYFSKKTNDI

2. A modified SEB molecule according to claim 1, wherein said T-cell epitopes to be removed are located on one or more strings termed R1a,b,c, R2a and R3a of contiguous residues of the originally non-modified SEB molecule, the strings are selected from:

R1a: KFTGLMENMKVLYDD,

R1b: GLMENMKVLYDDNHV,or

R1c: ENMKVLYDDNHVSAI

R2a: SIKDTKLGNYDNVRV,

R3a: DKYVDVFGANYYYQC.

3. A modified SEB molecule according to claim 1 or 2, wherein the T-cell epitopes have been removed by substitution of one or more amino acid residues within said strings.

4. A modified molecule having the biological activity of staphylococcal enterotoxin B (SEB) and being substantially non-immunogenic or less immunogenic than any non-modified molecule having the same biological activity in an individual when used *in vivo*, wherein the said loss of immunogenicity is achieved by removing one or more T-cell epitopes derived from the originally non-modified molecule and said T-cell epitopes are MHC class II ligands or peptide sequences which show the ability to stimulate or bind T-cells via presentation on class II, said modified molecule comprises the sequence:
ESQPDPKPDELHKSSKFTGLX^{1}ENX^{2}KVLX^{3}DDNHVSAINVKSIDQFLYFDLIYSX^{4}K
DTKX^{5}GNYDNVRVEFKNKDLADKYKDKX^{6}X^{7}DX^{8}X^{9}GANYYYQCYFSKKTNDINS
HQTDKRKTCMYGGVTEHNGNQLDKYRSITVRVFEDGKNLLSFDVQTNKKKVTA
QELDYLTRHYLVKNKKLYEFNNSPYETGYIKFIENENSFWYDMMPAPGDKFDQS
KYLMMYNDNKMVDSKDVKIEVYLTTKKK, wherein
X^1 = A, G, P or M;
X^2 = A, G, P, or M;
X^3 = T, A, D, E, G, H, K N, P, Q, R, S, or Y;
X^4 = A, or I;
X^5 = H, or L;
X^6 = T, A, D, E, G, H, K N, P, Q, R, S, or Y;
X^7 = H, or V;
X^8 = A, P, G, or V;
X^9 = T, H, or F;
whereby simultaneously X^1 = M, X^2 = M, X^3 = Y, X^4 = Y, X^5 = L, X^6 = Y, X^7 = V, X^8 = V and X^9 = F are excluded.

5. A modified SEB molecule of claim 4, wherein X^1 = A, X^2 = A, X^3 = T, X^4 = A, X^5 = H, X^6 = T, X^7 = H, X^8 = A, and X^9 = T.

6. A modified SEB molecule of claim 4 or 5, wherein the molecule, when tested as a whole protein in a biological T-cell proliferation assay, exhibits a stimulation index (SI) smaller than the parental non-modified SEB molecule and smaller than 2.

7. A DNA molecule coding for a modified SEB molecule as specified in any of the claims 1 to 6.

8. A pharmaceutical composition comprising a modified SEB molecules as specified in any of the claims 1 to 7 together with a pharmaceutically acceptable carrier, diluent or excipient.

9. A peptide sequence being part of a molecule having the biological activity of staphylococcal enterotoxin B (SEB) and comprising one or more T-cell epitopes being MHC class II ligands or sequence tracks which show the ability to stimulate or bind T-cells via presentation on class II; the peptide is selected from Table 1 or Table 2.

10. A peptide sequence according to claim 9, comprising 13 to 15 consecutive amino acid residues from any of said strings.

11. A peptide sequence according to claim 9 or 10 exhibiting, when tested in a biological human T-cell proliferation assay, a stimulation index (SI) greater than 2.0.

12. A modified peptide sequence of claim 11, wherein the modification results in eliminating potential T-cell epitopes being MHC class II ligands by substitution of one or more amino acid residues, the peptide exhibits, when tested in a biological human T-cell proliferation assay, a stimulation index (SI) smaller than 2.0, preferably 1.8.

13. Use of a peptide according to claim 12 for the manufacture of a modified human SEB molecule as defined in claim 1.

14. A DNA molecule coding for a peptide sequence as specified in any of the claims 9 to 13.

15. A method of constructing a T-cell epitope map of staphylococcal enterotoxin B (SEB) by locating T-cell epitopes in unmodified SEB, the method comprising the steps:

(i) in-vitro antigen stimulation using synthetic peptide immunogens using PBMC preparations from unrelated donor samples containing physiologic ratios of T-cell to antigen presenting cells,

(ii) applying computational schemes that simulate the binding of the peptide ligand with one or more MHC allotypes in order to analyse the epitope regions identified in step (i) and thereby identifying MHC class II ligands within the epitope regions;

(iii) applying computational schemes simulating the binding of the peptide ligand with one or more MHC allotypes to identify sequence analogues of the MHC ligands encompassed within the epitope region(s) which no longer bind MHC class II or bind with lowered affinity to a lesser number of MHC allotypes; and optionally

(iv) using naïve T-cell activation assays and synthetic peptides encompassing entirely or in collection encompassing the epitope regions identified within the SEB molecule and testing the sequence analogues in naïve T-cell activation assay in parallel with the parental SEB sequences.

16. A method of claim 15, wherein the location of a specific T-cell epitope is found when a stimulation index (SI) of 2.0 or greater is observed in at least two independent donor samples.